



# UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE  
United States Patent and Trademark Office  
Address: COMMISSIONER FOR PATENTS  
P.O. Box 1450  
Alexandria, Virginia 22313-1450  
[www.uspto.gov](http://www.uspto.gov)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/566,776	10/02/2006	Andrew V. Schally	SHAL3.0-032PCT/US	7750
47375	7590	10/29/2007	EXAMINER	
OMRI M. BEHR			HA, JULIE	
325 PIERSON AVENUE			ART UNIT	PAPER NUMBER
EDISON, NJ 08837-3123			1654	
		MAIL DATE	DELIVERY MODE	
		10/29/2007	PAPER	

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/566,776	SCHALLY ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Julie Ha	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 28 August 2007.
- 2a) This action is FINAL.                    2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 1-7 and 16-28 is/are pending in the application.
  - 4a) Of the above claim(s) 6 and 7 is/are withdrawn from consideration.
- 5) Claim(s) 1-4, 16-20 and 22 is/are allowed.
- 6) Claim(s) 5 and 21 is/are rejected.
- 7) Claim(s) 23-28 is/are objected to.
- 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
  - a) All    b) Some \* c) None of:
    1. Certified copies of the priority documents have been received.
    2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
    3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413)
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	Paper No(s)/Mail Date. _____.
3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)	5) <input type="checkbox"/> Notice of Informal Patent Application
Paper No(s)/Mail Date _____.	6) <input type="checkbox"/> Other: _____.

**DETAILED ACTION**

Response to Election filed on August 28, 2007 is acknowledged. Claims 8-15 have been cancelled. Claims 1-7 and 16-28 are pending in this application.

***Restriction***

1. Applicant's election with traverse of species election of peptide sequence number 96 in the reply filed on August 28, 2007 is acknowledged. The traversal is on the ground(s) that species are sufficiently linked to comply with unity requirement. This is not found persuasive because the hGH-RH has 29 amino acid residues and 18 out of the 29 amino acids are different from the wild-type hGH-RH sequence. This implies that there is about 38% homology to the wild-type hGH-RH sequence. Since there are 20 naturally occurring amino acids,  $18^{20} = 4.9 * 10^{18}$  different hGH-RH possibilities. Additionally, there are non-naturally occurring amino acids, such as D-isomers,  $\beta$ -amino acid,  $\varepsilon$ -amino acids and  $\gamma$ -amino acids, as well as amino acid mimetics. Having a sequence homology of 38% does not correspond to the "core" of the amino acid sequence. Therefore, the invention lacks unity.

2. The requirement is still deemed proper and is therefore made FINAL. A search was conducted on the elected peptide sequence, 96, and this was deemed free of prior art. A search was extended to the other species in claims 3-4 and these too were found to be free of prior art. A search was extended to species disclosed in claim 5, and a prior art was found. Claims 6-7 are withdrawn from further consideration as

being drawn to nonelected species. Claims 1-5 and 16-28 are examined on the merits in this office action.

***Objection-Minor Informalities***

3. The specification is objected to because of the following minor informality: There appears to be a spelling error at Example XII heading. The “Oncolocical” should be corrected to “Oncological”.

***Duplicate Claims***

4. Applicant is advised that should claim 22 be found allowable, claims 23-28 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claim 22 is drawn to a pharmacologically administrable composition and a pharmacologically acceptable carrier, and claims 23-28 are drawn to a pharmacologically administrable composition and a pharmacologically acceptable carrier. Claims 23-28 does not further limit claim 22, since claims 22-28 are all drawn to a pharmacologically administrable composition and a pharmacologically acceptable carrier. Therefore, claims 23-28 are substantial duplicates of claim 22.

***Rejection-35 U.S.C. 112, 2<sup>nd</sup>***

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claim 1 recite, "A<sup>0</sup> is Phe, D-Phe, Arg, D-Arg, or a carbon-nitrogen single bond" (at line13) and "A<sup>30</sup> is Arg, D-Arg, Har, D-Har, Cit, D-Cit, Arm, or is a carbon-nitrogen or carbon-oxygen single bond" (at lines 33-34). These phrases are unclear. It is unclear if "carbon-nitrogen single bond" is part of R<sub>1</sub> or if carbon-nitrogen bond is additional carbon-nitrogen linkage in between R<sub>1</sub> and A<sup>1</sup>. Additionally, it is unclear if "carbon-nitrogen or carbon-oxygen single bond" is part of A<sup>29</sup> amino acid or is in addition to the peptide linkage in between A<sup>29</sup> and R<sub>2</sub>.

***Rejection-35 U.S.C. 112, 1<sup>st</sup>***

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claim 21 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *in vitro* activity, does not reasonably provide enablement for *in vivo* activity. The specification does not enable any person skilled in

the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature or the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

*(1) The nature of the invention:*

The invention relates to synthetic peptides that inhibit the release of growth hormone from the pituitary in mammals as well as inhibit the proliferation of human cancer through a direct effect on the cancer cells, and to therapeutic compositions containing these peptides.

*(2) The state of the prior art:*

Voskoglou-Monikos et al (Clinical Cancer Research, 2003, 9: 4227-4239) indicates that both basic science studies and clinical trials are essential components of the cancer drug discovery process (see p. 4227, right column, 1<sup>st</sup> paragraph). Further,

the reference indicates that advancing of a candidate drug from preclinical testing in the lab to testing in Phase II clinical trials is based on the assumption that drug activity in cancer models translate into at least some efficacy in human patients (i.e., that cancer laboratory models are clinically predictive) (see p. 4227, right column, 2<sup>nd</sup> paragraph). Furthermore, the reference indicates that all studies aimed to examine the clinical predictive value of laboratory cancer models inevitably suffer from inherent bias because compounds with no activity in preclinical models are generally not advanced to clinical trials (see p. 4227, 3<sup>rd</sup> paragraph). The reference discloses a examination of clinical predictive value of three widely used preclinical cancer models, namely, the in vitro human tumor cell line, the human xenograft, and the murine allograft models. These experiments were conducted on breast, NSCLC, ovary and colon cancers (see p. 4234, right column, 1<sup>st</sup> full paragraph). The reference discloses that in vitro cell line model was found to be predictive of Phase II performance for non-small cell lung cancer (NSCLC) under the disease-oriented approach, for breast and ovarian cancers under the compound-oriented approach, and in the case of all four tumor types together (see abstract and p. 4235, right column). The reference further indicates that the murine allograft model is not predictive of clinical Phase II performance (see abstract and p. 4236, left column, 3<sup>rd</sup> paragraph). Further, the reference indicates that human xenograft model showed good tumor-specific predictive value for NSCLC and ovarian cancers when panels of xenografts were used. However, it failed to adequately predict clinical performance for breast and colon tumors (see abstract and p. 4236, right column, 1<sup>st</sup> paragraph).

Art Unit: 1654

In regards to "inhibiting angiogenesis or lymphangiogenesis", Auerbach et al (Cancer and Metastasis Reviews, 2000, 19: 167-172) indicates that one of the major problems in angiogenesis research has been the difficulty of finding suitable methods for assessing the angiogenic response (see p. 167, left column, 1<sup>st</sup> paragraph). The prior art further indicates that the chick embryo total explant assay was designed to permit sequential photography during the angiogenesis response to tumor cells. Auerbach et al further indicates that one of the major problems in angiogenesis research has been the difficulty of finding suitable methods for assessing the angiogenic response. For example, the 96 well rapid screening assay for cytokinesis was developed in order to permit screening of hybridoma supernatants... *In vitro* tests in general have been limited by the availability of suitable sources for endothelial cells, while *in vivo* assays have proven difficult to quantitate, limited in feasibility, and the test sites are not typical of the *in vivo* reality (see p. 167, left column, 1<sup>st</sup> paragraph). Furthermore, the reference indicates that the *in vitro* assays can be exceedingly useful in screening for specific functions; however, these assays frequently do not translate into effects on angiogenesis *in vivo* because of the complex nature of *in vivo* angiogenesis (see p. 167, right column, 2<sup>nd</sup> paragraph). The reference indicates that a serious problem *in vitro* assays utilizing endothelial cells is the difficulty in obtaining adequate numbers of primary isolates. There are significant changes during prolonged culture, including alterations in activation state, karyotype, expression of cell surface antigens and growth properties, and this presents a significant impediment to using these cells as a model for *in vivo* reactions because endothelial cells are normally in a

quiescent state (see p. 168, left column, 2<sup>nd</sup> paragraph). Additionally, another problem is the fact that all endothelial cells are not alike, and that the response to growth factors and inhibitors varies with the source of these endothelial cells. Microvascular endothelial cells, the primary responding cells during angiogenesis, differ for different organs, within different blood vessels of those organs and even within individual blood vessels (see p. 168, left column, top of 3<sup>rd</sup> paragraph). Furthermore, prior art indicates the difficulties in going from *in vitro* to *in vivo* for drug development for inhibition of angiogenesis. Furthermore, the reference indicates that there is heterogeneity even among tumor-associated endothelial cells, as can be readily demonstrated by experiments which show that different tumors show a highly selective capacity to adhere to organ and site-specific blood vessels. Moreover, different endothelial cells produce different cytokines, thus introducing yet more complexity into the assay systems. *In vitro* model systems that fail to take this marked diversity among endothelial cells into account are likely to miss many of the fine points underlying the *in vivo* angiogenic response (see p. 168, left column, bottom of 3<sup>rd</sup> paragraph). Furthermore, the reference indicates that there are two aspects of cell culture assays involving endothelial cells that are readily apparent but frequently overlooked: 1) endothelial cells are difficult to maintain and hence readily inhibited or killed, although such endothelial cells are rugged and long-lived *in vivo*. The slightest change in pH or osmolarity is cytotoxic to endothelial cells *in vitro*, thus, may agents may prove to have efficacy in preventing endothelial cell growth, migration or structural rearrangement *in vitro* for reasons that have no relevancy to angiogenesis *in vivo* (most important in testing anti-angiogenic factors); 2) there are numerous cytotoxic

Art Unit: 1654

agents and growth factors that are not specific to endothelial cells at all, and thus are unlikely to have selective effects on angiogenesis *in vivo* (see p. 168, right column, 2<sup>nd</sup> paragraph). Furthermore, the reference indicates that methods for culture of whole avian or mammalian embryos have only limited application in assessing angiogenesis, primarily because these explanted embryos do not survive for more than a few days, and the principal use for mammalian and avian whole embryo cultures has been to study short-term effects of agents or of transgene expression, with the focus on vasculogenesis and organ formation (p. 169, left column, 2<sup>nd</sup> paragraph). When utilizing explanted chick embryo, much caution needs to be exercised, when evaluating CAM grafts, since the CAM is itself a rapidly growing organ with an expanding vasculature, which may obscure any pro-angiogenic effect. Any agent that causes local edema will appear to be anti-angiogenic at the test site (see p. 169, left column, 3<sup>rd</sup> paragraph). The reference further indicates that there are some problems with the mouse corneal angiogenesis assay. The fact that the cornea is avascular makes it atypical: Angiogenesis *in vivo* does not normally occur in avascular regions. The corneal pocket itself is exempt from the many blood-borne factors that can influence endothelial cell maintenance or survival (see p. 169, right column, 2<sup>nd</sup> paragraph). Further, the Matrigel plug assay unfortunately has considerable variability in the assay, largely because it is difficult to generate identical three-dimensional plugs even though the total Matrigel volume is kept constant (see p. 170, left column, 4<sup>th</sup> paragraph).

Jain et al (Nature Medicine, 1997, 3(11): 1203-1208) additionally indicate that there are several key questions remain unanswered in quantitative angiogenesis

assays:... 5) what is the relative role of biochemical versus mechanical microenvironment in angiogenesis?... 7) what novel pharmaceutical agents can inhibit or stimulate angiogenesis in a clinical setting?; 8) what are the optimal dose and schedule of these agents? (see p. 1203, left column, bottom of the 2<sup>nd</sup> paragraph and right column, 1<sup>st</sup> paragraph). The reference further indicates that a common problem associated with various in vivo assays of vascularization into matrix implants is the nonspecific host response to the matrix implantation. A significant angiogenic response has been observed without any stimulation by exogenous growth factors, and only the amount of angiogenesis relative to the controls should be considered as the response to the exogenous angiogenic factors (see p. 1206, right column, 2<sup>nd</sup> paragraph). The reference further indicates that angiogenesis in vivo can be assessed qualitatively through the measurement of the plasma or urine concentration of angiogenic factors...the number of vessels in tumors or wound sites may thus not necessarily correlate with the plasma or urine concentration of angiogenic factors (see p. 1206, left column, 4<sup>th</sup> paragraph). Further, the reference indicates that the reagents (endothelial cell origin and passage number, collagen or Matrigel substrate, growth media, angiogenic agents, level of endotoxin) have not been standardized enough to permit inter-lab quantitative comparison. Furthermore, any molecule promoting or inhibiting the endothelial cell movement, proliferation or differentiation in vitro may not necessarily evoke the same response in vivo. Hence, caution must be exercised in the extrapolation of in vitro observations to the in vivo situation (see p 1207, left column, 1<sup>st</sup> paragraph).

Additionally, those of skill in the art recognize that *in vitro* assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the *in vivo* environment as compared to the very narrowly defined and controlled conditions of an *in vitro* assay does not permit a single extrapolation of *in vitro* assays to human diagnostic efficacy with any reasonable degree of predictability. *In vitro* assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (*Culture of Animal Cells, A Manual of Basic Technique*, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see *Major Differences In Vitro*). Further, Dermer (*Bio/Technology*, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer teaches that

Art Unit: 1654

when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

Further, both the treatment of cancer and or inhibition of angiogenesis in a host are quite unpredictable. For example, it was recently revealed that the drug Endostatin is unlikely to be the kind of across-the-board cancer cure that many had hoped for. Out of the 61 terminally ill patients tested, not one recovery had been seen (MSNBC News Services, "Mixed results on new cancer drug", November 9, 2000). Hence, it would not be predictable that a method drawn to inhibiting angiogenesis would be effective in a host in need thereof- such as a host suffering from cancer. Further, treatment of cancer in general is at most unpredictable, as underscored by Gura (Science, v278, 1997, pp.1041-1042) who discusses the potential shortcomings of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to

Art Unit: 1654

supportive care, have won approval from the FDA (page 1041, 1<sup>st</sup> column) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive. Lastly, with regards to the prevention of metastasis, the specification lacks the critical steps necessary in presenting some type of predictable response in a population of hosts deemed necessary to prevent metastasis. Reasonable guidance with respect to preventing any cancer relies on quantitative analysis from defined populations which have been successfully pre-screened and are predisposed to particular types of cancer. This type of data might be derived from widespread genetic analysis, cancer clusters, or family histories. The essential element towards the validation of a preventive therapeutic is the ability to test the drug on subjects monitored in advance of clinical cancer and *link* those results with subsequent histological confirmation of the presence or absence of disease. This irrefutable link between antecedent drug and subsequent knowledge of the prevention of the disease is the essence of a valid preventive agent. Further, a preventive administration also must assume that the therapeutic will be safe and tolerable for anyone susceptible to the disease. All of this underscores the criticality of providing workable examples which is not disclosed in the specification, particularly in an unpredictable art, such as cancer therapy.

The art recognizes the problems in angiogenesis research and the difficulties in extrapolating the *in vitro* data to *in vivo* situations. In view of the teachings above, and the lack of guidance and or exemplification in the specification, it would not be

predictable that the method would function as contemplated. Thus, it would require undue experimentation by one of skill in the art to practice the invention as claimed.

*(3) The relative skill of those in the art:*

The relative skill of those in the art is high.

*(4) The predictability or unpredictability of the art:*

Applicant's activity is based on biological activity in endocrine and oncological assays on in vitro system and on various cancer models in vivo (such as tumors grown in nude mice). Furthermore, the claim is drawn to a method of the treatment of a patient having a cancer carrying receptors for GH-RH by administering to the patient an effective amount of synthetic compound to block the GH-RH receptors. Applicant's activity is based on the fact that claimed compounds can block the GH-RH receptors. However, this GH-RH receptor inhibition must be measured somehow from the patient being administered the said compound. As described above, it is difficult to extrapolate the *in vitro* data to *in vivo* situations. There are too many variables between the experimentation, thus, it clearly shows the unpredictability of the art.

*(5) The breadth of the claims:*

The claim is drawn to a method of treatment of a patient having a cancer carrying receptors for GH-RH by administering to said patient an amount of a compound of synthetic hGH-RH antagonists (claim 1) effective to block said GH-RH receptors.

(6) *The amount of direction or guidance presented and (7) The presence or absence of working examples:*

Examples I through VIII describe the methods of synthesizing the peptide hGH-RH peptide antagonists. Examples IX through XI describe the methods of making the injectable formulation. Example XII discloses the biological activity in endocrine and oncological assays using superfused rat pituitary system (in vitro) and measuring the GH levels in aliquots of undiluted and diluted superfusion samples. Example further discloses blood samples, tumors are collected from rat. Furthermore, the example describes ligand competition assays with <sup>125</sup>I-labeled GH-RH antagonist JV-1-42 were used to determine the binding affinities of GH-RH analogs to the GH-RH receptor isoforms on membrane fractions of human PC-3 prostate tumors (see paragraph [0342]). Example VII further discloses the effect of GH-RH antagonists on PC-3 human prostate cancer xenografts in nude mice experiment, and these experiments measured the tumor volumes (see paragraphs [0345]-[0358]). For example, paragraph [0346] and Table VII discloses the suppression of IGF-I levels in the serum and IGF-II levels in the tumors with GH-RH antagonist treatment on nude mice xenografts of PC-3 human prostate cancer. Although the specification provides guidance on how to measure the inhibition/suppression of tumor growth, it does not provide guidance as how to measure the GH-RH receptor inhibition without looking at the tumor mass and cells.

As described supra, Voskoglou-Monikos et al (Clinical Cancer Research, 2003, 9: 4227-4239) indicates that both basic science studies and clinical trials are essential components of the cancer drug discovery process (see p. 4227, right column, 1<sup>st</sup>

paragraph). Further, the reference indicates that advancing of a candidate drug from preclinical testing in the lab to testing in Phase II clinical trials is based on the assumption that drug activity in cancer models translate into at least some efficacy in human patients (i.e., that cancer laboratory models are clinically predictive) (see p. 4227, right column, 2<sup>nd</sup> paragraph). Furthermore, the reference indicates that all studies aimed to examine the clinical predictive value of laboratory cancer models inevitably suffer from inherent bias because compounds with no activity in preclinical models are generally not advanced to clinical trials (see p. 4227, 3<sup>rd</sup> paragraph). The reference discloses a examination of clinical predictive value of three widely used preclinical cancer models, namely, the in vitro human tumor cell line, the human xenograft, and the murine allograft models. These experiments were conducted on breast, NSCLC, ovary and colon cancers (see p. 4234, right column, 1<sup>st</sup> full paragraph). The reference discloses that in vitro cell line model was found to be predictive of Phase II performance for non-small cell lung cancer (NSCLC) under the disease-oriented approach, for breast and ovarian cancers under the compound-oriented approach, and in the case of all four tumor types together (see abstract and p. 4235, right column). The reference further indicates that the murine allograft model is not predictive of clinical Phase II performance (see abstract and p. 4236, left column, 3<sup>rd</sup> paragraph). Further, the reference indicates that human xenograft model showed good tumor-specific predictive value for NSCLC and ovarian cancers when panels of xenografts were used. However, it failed to adequately predict clinical performance for breast and colon tumors (see abstract and p. 4236, right column, 1<sup>st</sup> paragraph).

In regards to "inhibiting angiogenesis or lymphangiogenesis", Auerbach et al (Cancer and Metastasis Reviews, 2000, 19: 167-172) indicates that one of the major problems in angiogenesis research has been the difficulty of finding suitable methods for assessing the angiogenic response (see p. 167, left column, 1<sup>st</sup> paragraph). The prior art further indicates that the chick embryo total explant assay was designed to permit sequential photography during the angiogenesis response to tumor cells. Auerbach et al further indicates that one of the major problems in angiogenesis research has been the difficulty of finding suitable methods for assessing the angiogenic response. For example, the 96 well rapid screening assay for cytokinesis was developed in order to permit screening of hybridoma supernatants... *In vitro* tests in general have been limited by the availability of suitable sources for endothelial cells, while *in vivo* assays have proven difficult to quantitate, limited in feasibility, and the test sites are not typical of the *in vivo* reality (see p. 167, left column, 1<sup>st</sup> paragraph). Furthermore, the reference indicates that the *in vitro* assays can be exceedingly useful in screening for specific functions, however, these assays frequently do not translate into effects on angiogenesis *in vivo* because of the complex nature of *in vivo* angiogenesis (see p. 167, right column, 2<sup>nd</sup> paragraph). The reference indicates that a serious problem *in vitro* assays utilizing endothelial cells is the difficulty in obtaining adequate numbers of primary isolates. There are significant changes during prolonged culture, including alterations in activation state, karyotype, expression of cell surface antigens and growth properties, and this presents a significant impediment to using these cells as a model for *in vivo* reactions because endothelial cells are normally in a

Art Unit: 1654

quiescent state (see p. 168, left column, 2<sup>nd</sup> paragraph). Additionally, another problem is the fact that all endothelial cells are not alike, and that the response to growth factors and inhibitors varies with the source of these endothelial cells. Microvascular endothelial cells, the primary responding cells during angiogenesis, differ for different organs, within different blood vessels of those organs and even within individual blood vessels (see p. 168, left column, top of 3<sup>rd</sup> paragraph). Furthermore, prior art indicates the difficulties in going from *in vitro* to *in vivo* for drug development for inhibition of angiogenesis.

Furthermore, the reference indicates that there is heterogeneity even among tumor-associated endothelial cells, as can be readily demonstrated by experiments which show that different tumors show a highly selective capacity to adhere to organ and site-specific blood vessels. Moreover, different endothelial cells produce different cytokines, thus introducing yet more complexity into the assay systems. *In vitro* model systems that fail to take this marked diversity among endothelial cells into account are likely to miss many of the fine points underlying the *in vivo* angiogenic response (see p. 168, left column, bottom of 3<sup>rd</sup> paragraph). Furthermore, the reference indicates that there are two aspects of cell culture assays involving endothelial cells that are readily apparent but frequently overlooked: 1) endothelial cells are difficult to maintain and hence readily inhibited or killed, although such endothelial cells are rugged and long-lived *in vivo*. The slightest change in pH or osmolarity is cytotoxic to endothelial cells *in vitro*, thus, may agents may prove to have efficacy in preventing endothelial cell growth, migration or structural rearrangement *in vitro* for reasons that have no relevancy to angiogenesis *in vivo* (most important in testing anti-angiogenic factors); 2) there are numerous cytotoxic

agents and growth factors that are not specific to endothelial cells at all, and thus are unlikely to have selective effects on angiogenesis *in vivo* (see p. 168, right column, 2<sup>nd</sup> paragraph). Furthermore, the reference indicates that methods for culture of whole avian or mammalian embryos have only limited application in assessing angiogenesis, primarily because these explanted embryos do not survive for more than a few days, and the principal use for mammalian and avian whole embryo cultures has been to study short-term effects of agents or of transgene expression, with the focus on vasculogenesis and organ formation (p. 169, left column, 2<sup>nd</sup> paragraph). When utilizing explanted chick embryo, much caution needs to be exercised, when evaluating CAM grafts, since the CAM is itself a rapidly growing organ with an expanding vasculature, which may obscure any pro-angiogenic effect. Any agent that causes local edema will appear to be anti-angiogenic at the test site (see p. 169, left column, 3<sup>rd</sup> paragraph). The reference further indicates that there are some problems with the mouse corneal angiogenesis assay. The fact that the cornea is avascular makes it atypical: Angiogenesis *in vivo* does not normally occur in avascular regions. The corneal pocket itself is exempt from the many blood-borne factors that can influence endothelial cell maintenance or survival (see p. 169, right column, 2<sup>nd</sup> paragraph). Further, the Matrigel plug assay unfortunately has considerable variability in the assay, largely because it is difficult to generate identical three-dimensional plugs even though the total Matrigel volume is kept constant (see p. 170, left column, 4<sup>th</sup> paragraph).

Jain et al (Nature Medicine, 1997, 3(11): 1203-1208) additionally indicate that there are several key questions remain unanswered in quantitative angiogenesis

Art Unit: 1654

assays:... 5) what is the relative role of biochemical versus mechanical microenvironment in angiogenesis?... 7) what novel pharmaceutical agents can inhibit or stimulate angiogenesis in a clinical setting?; 8) what are the optimal dose and schedule of these agents? (see p. 1203, left column, bottom of the 2<sup>nd</sup> paragraph and right column, 1<sup>st</sup> paragraph). The reference further indicates that a common problem associated with various in vivo assays of vascularization into matrix implants is the nonspecific host response to the matrix implantation. A significant angiogenic response has been observed without any stimulation by exogenous growth factors, and only the amount of angiogenesis relative to the controls should be considered as the response to the exogenous angiogenic factors (see p. 1206, right column, 2<sup>nd</sup> paragraph). The reference further indicates that angiogenesis in vivo can be assessed qualitatively through the measurement of the plasma or urine concentration of angiogenic factors... the number of vessels in tumors or wound sites may thus not necessarily correlate with the plasma or urine concentration of angiogenic factors (see p. 1206, left column, 4<sup>th</sup> paragraph). Further, the reference indicates that the reagents (endothelial cell origin and passage number, collagen or Matrigel substrate, growth media, angiogenic agents, level of endotoxin) have not been standardized enough to permit inter-lab quantitative comparison. Furthermore, any molecule promoting or inhibiting the endothelial cell movement, proliferation or differentiation in vitro may not necessarily evoke the same response in vivo. Hence, caution must be exercised in the extrapolation of in vitro observations to the in vivo situation (see p 1207, left column, 1<sup>st</sup> paragraph).

Additionally, those of skill in the art recognize that *in vitro* assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the *in vivo* environment as compared to the very narrowly defined and controlled conditions of an *in vitro* assay does not permit a single extrapolation of *in vitro* assays to human diagnostic efficacy with any reasonable degree of predictability. *In vitro* assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (*Culture of Animal Cells, A Manual of Basic Technique*, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see *Major Differences In Vitro*). Further, Dermer (*Bio/Technology*, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer teaches that

when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

Further, both the treatment of cancer and or inhibition of angiogenesis in a host are quite unpredictable. For example, it was recently revealed that the drug Endostatin is unlikely to be the kind of across-the-board cancer cure that many had hoped for. Out of the 61 terminally ill patients tested, not one recovery had been seen (MSNBC News Services, "Mixed results on new cancer drug", November 9, 2000). Hence, it would not be predictable that a method drawn to inhibiting angiogenesis would be effective in a host in need thereof- such as a host suffering from cancer. Further, treatment of cancer in general is at most unpredictable, as underscored by Gura (Science, v278, 1997, pp.1041-1042) who discusses the potential shortcomings of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to

Art Unit: 1654

supportive care, have won approval from the FDA (page 1041, 1<sup>st</sup> column) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive. Lastly, with regards to the prevention of metastasis, the specification lacks the critical steps necessary in presenting some type of predictable response in a population of hosts deemed necessary to prevent metastasis. Reasonable guidance with respect to preventing any cancer relies on quantitative analysis from defined populations which have been successfully pre-screened and are predisposed to particular types of cancer. This type of data might be derived from widespread genetic analysis, cancer clusters, or family histories. The essential element towards the validation of a preventive therapeutic is the ability to test the drug on subjects monitored in advance of clinical cancer and *link* those results with subsequent histological confirmation of the presence or absence of disease. This irrefutable link between antecedent drug and subsequent knowledge of the prevention of the disease is the essence of a valid preventive agent. Further, a preventive administration also must assume that the therapeutic will be safe and tolerable for anyone susceptible to the disease. All of this underscores the criticality of providing workable examples which is not disclosed in the specification, particularly in an unpredictable art, such as cancer therapy.

There is no clear guidance as to how to measure the GH-RH receptor inhibition, since angiogenesis *in vivo* can be assessed through the measurement of the plasma or urine concentration of angiogenic factors, but the number of vessels in tumors or wound sites may thus not necessarily correlate with the plasma or urine concentration of

Art Unit: 1654

angiogenic factors (see Jain et al, p. 1206, right column, last paragraph). Since wound can increase the angiogenic factors *in vivo* and it is unclear who would develop tumors, more guidance is necessary. Since the prior art recognizes the difficulties in extrapolating the *in vitro* data to *in vivo* situations, more guidance is necessary.

*(8) The quantity of experimentation necessary:*

Since it is uncertain to predict and correlate *in vitro* data to *in vivo* system, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to determine if the hGH-RH peptide antagonists would be effective in preventing angiogenesis, lymphangiogenesis and GH-RH receptor inhibition *in vivo*, and thus preventing tumors *in vivo*.

***Rejection-35 U.S.C. 102***

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claim 5 is rejected under 35 U.S.C. 102(b) as being anticipated by Schally et al (US Patent # 6057422).

12. The instant claims are drawn to a compound consisting of peptide sequence of Peptide 27 (PhAc-Tyr<sup>1</sup>, D-Arg<sup>2</sup>, Phe(pCl)<sup>6</sup>, Abu<sup>8</sup>, Arg<sup>9</sup>, Abu<sup>15</sup>, Nle<sup>27</sup>, D-Arg<sup>28</sup>, Har<sup>29</sup>]hGH-RH(1-29)NH<sub>2</sub>.

13. Schally et al teach hGH-RH(1-29)NH<sub>2</sub> peptide analogs that inhibit the activity of endogenous hGH-RH activity comprising of the formula: X-R<sup>1</sup>-R<sup>2</sup>-Asp-Ala-R<sup>5</sup>-Thr-R<sup>8</sup>-R<sup>9</sup>-R<sup>10</sup>-Arg-R<sup>12</sup>-R<sup>13</sup>-R<sup>14</sup>-R<sup>15</sup>-R<sup>16</sup>-Leu-R<sup>18</sup>-R<sup>19</sup>-Arg-R<sup>21</sup>-R<sup>22</sup>-Leu-Gln-Asp-Ile-R<sup>27</sup>-R<sup>28</sup>-R<sup>29</sup>-NH<sub>2</sub>. The reference teaches that X is PhAc, R<sup>2</sup> is D-Arg, R<sup>6</sup> is Phe(pCl), R<sup>8</sup> is Abu, R<sup>9</sup> is Arg, R<sup>15</sup> is Abu, R<sup>27</sup> is Nle, R<sup>28</sup> is D-Arg and R<sup>29</sup> is Har (see column 2, lines 60-67 and column 3, lines 1-29). Therefore, this meets the limitation of claim 5. Claims 6-7 have been withdrawn because the elected species do not read on claims 6-7.

### ***Conclusion***

14. Claims 1-4, 16-20 and 22 are allowable, because the peptide sequences of hGH-RH(1-29) antagonists are free of prior art. The closest art found was Schally et al (US Patent # 6057422) and Schally et al (US Patent # 7026281), but the peptides of these prior art teach that at R<sup>9</sup> is selected from Arg, Har, Lys, Orn, D-Arg, D-Har, D-Lys, D-Orn, Cit, Nle, Tyr(Me), Ser, Ala or Aib. The peptides of the instant claims 1-4 disclose that A<sup>9</sup> (same position as R<sup>9</sup>) is selected from His, D-His, Amp, D-Amp, Gup or D-Gup. Therefore, the peptides of claims 1-4 are both novel and unobvious over the prior art of record.

Art Unit: 1654

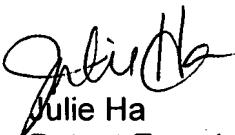
15. Claims 5 and 21 are rejected. Claims 23-28 have been objected to since these claims are substantial duplicates of claim 22. Claims 6-8 have been withdrawn, as being drawn to nonelected species.

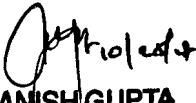
16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Julie Ha whose telephone number is 571-272-5982.

The examiner can normally be reached on Mon-Fri, 8:00 am to 4:30 pm.

17. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

18. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

  
Julie Ha  
Patent Examiner  
AU 1654

  
ANISH GUPTA  
PRIMARY EXAMINER

### **EXAMINER'S AMENDMENT**

1. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.
2. Authorization for this examiner's amendment was given in a telephone interview with Mr. Omri H. Behr on XXX.
3. Claims 5-7 and 21 have been cancelled. Claims 1-4, 16-20 and 22-28 are allowed.
4. The application has been amended as follows:

Claim 1: At line 13, delete "a carbon-nitrogen single bond".

At lines 33-34, delete "or is a carbon-nitrogen or carbon-oxygen single bond".

### ***Reasons for Allowance***

5. The following is an examiner's statement of reasons for allowance: The hGH-RH(1-29) analogs claimed are both novel and unobvious over the prior art. The closest prior art are as follows: US Patent # 6057422 teaches a synthetic analogs of hGH-RH(1-29)NH<sub>2</sub>, wherein the amino acid at positions 9 and 28 are both Serine (see Claim 1). US Patent # 7026281 teaches a series of synthetic analogs of hGH-RH(1-29)NH<sub>2</sub>, wherein the analogs inhibit the activity of endogenous hGH-RH and prevent the release

Art Unit: 1654

of growth hormone (see abstract). The reference teaches a hGH-RH analog having serine at positions 9 and 28 as US Patent # 6057422, and teaches a method of suppressing excessive levels of GH in a patient in need thereof, comprising administering to the patient in need an effective amount of the hGH-RH peptide analog (see abstract and claims 1-9). The claimed peptide analogs of instant application are novel and unobvious over the prior art known in the art.

6. Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

***Conclusion***

7. Claims 1-4, 16-20 and 22-28 are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Julie Ha whose telephone number is 571-272-5982. The examiner can normally be reached on Mon-Fri, 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1654

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Julie Ha  
Patent Examiner  
AU 1654